REMARKS

Applicants have canceled claims 39, 45, 46, 50-62 and 64 from the application without prejudice or disclaimer as directed to a non-elected invention which has been withdrawn from consideration. Applicants retain all rights to filing a divisional application including the non-elected subject matter. The obvious typographical errors in claims 38 and 63 (noted by the Examiner) have been corrected thereby obviating any objection to these claims . The claims now remaining in the application are claims 38(amended), 40-44, 47-49 and 63(amended). Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 USC 112 and are clearly patentable over the references of record.

The rejection of claims 38, 40-44, 47-49 and 63 under 35 U.S.C. 103(a) as being unpatentable over either one of Quay or Unger in view of Schneider and Martin have been carefully considered but are most respectfully traversed. Applicants most respectfully submit that neither rejection renders the claimed subject matter prima facie obvious.

In this regard, Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C.103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

The references to Quay and Unger are the primary references relied upon in the rejection. With respect to the Quay (EP 727225) primary reference Applicants wish to point out that in contrast with the claims of the current application, Quay relates to phase transfer colloid systems. The disadvantages of such systems are discussed on page 3, lines 20-35, of the current patent application.

Quay relates to two main types of ultrasound agents both of which are targeted through the use of CAM ligands:

The first embodiment relates to surfactant-encapsulated microbubbles. The surfactants for use in these embodiments are said to be capable of being chosen from a vast list covering approximately 400-600 different surfactants (pages 4-6). No mention is made within this list, however, of phospholipid surfactants and no teaching toward such surfactants can be inferred from this list. More particularly, no mention is made within this list of the specific advantages to be obtained from the use of **monolayers** of surfactants. The use of such monolayers is a key feature of the present invention and is a claim limitation which cannot be ignored. The flexibility and deformability of such thin monolayer membranes substantially enhances the echogenicity of such reporters particularly relative to liposome systems containing bilayers or multiples of such bilayers. This may permit the use of very low doses of the reporter material to achieve high ultrasound contrast efficacy, with consequent safety benefits as would be appreciated by one of ordinary skill in the art.

The second embodiment of Quay relates to "a **solid** microsphere such as a proteinaceous microsphere" (page 4, lines 15-16, emphasis added). Clearly such microspheres are very different from those that are currently being claimed as would be appreciated by one of ordinary skill in the art.

Furthermore, there is nothing in Quay which, when taken alone or together with one or more of the other cited documents, would lead a skilled man in the art towards the specific combination of features claimed in the current claims. Consequently, it is respectfully asserted that the diagnostic agents of the current invention cannot be said to be obvious in the light of the disclosures made in Quay absent impermissible hindsight. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

The Official Action asserts that Unger makes reference to a number of the features of the current claims. It is respectfully pointed out, however, that the particular features identified by the Examiner are, in most cases, only to be found within long laundry lists of potentially-usable features. The necessary motivation is not present to make the necessary selection to arrive at the claimed invention. Obvious to try is not the standard of obviousness under 35 USC 103(a).

Applicants believe that under the interpretation that the US courts have given to 35 USC §103:

> "a citation may be relied upon for all that it would have **reasonably suggested** to one having ordinary skill in the art, including non-preferred embodiments".

Given the breadth of the disclosures in Unger, it is difficult to accept that this citation would have "reasonably suggested" any specific embodiments.

Whilst Unger refers to a number of different forms of "vesicle", the vast majority of the disclosures of this document refer to liposomes. The Examples (which are themselves "prophetic" - see column 29, lines 52-53) refer only to the production of liposomes, which, as can be seen from Example 3, possess "a single bilayer". Thus to the extent that Unger teaches the formation of any specific form of vesicle (which is not accepted by the Applicants), it appears to relate primarily to the production of liposomes possessing lipid **bilayers**.

It should particularly be noted that Unger does not discuss the specific advantages that can be obtained from the use of **monolayers** of film-forming surfactant which comprise phospholipid, as is claimed in the current claims.

The gas which forms part of the vesicles is said in Unger to be chosen from a wide variety of gases including air, noble gases, carbon dioxide, etc. as given on column 15, lines 7-20.

The main emphasis of Unger as far as the surfactant is concerned is directed to "**fluorinated** amphiphilic compounds". These are described at length from columns 7 to 11, *inter alia*.

Unger makes no reference to the covalent coupling of lipids to vectors, wherein the vectors bind to receptors/targets that are associated with angiogenesis,

inflammation, atherosclerotic plaques and/or thrombi in accordance with the present invention.

Accordingly, it is respectfully asserted that Unger would **not** have suggested to the skilled person the use of the very **specific combination of features** that are claimed in the current claims.

It is noted that the Examiner has conceded in this regard that:

> "Quay and Unger fail to specifically disclose the conjugation of antibodies to phospholipid membranes via a thiolated group as claimed" (middle of page 3).

The Examiner appears therefore to have cited Schneider and Martin in support of his assertion that such conjugation, *inter alia*, was well known in the art. With respect to Schneider (US 5,643,553), Applicants wish to note that this patent application is a divisional of US 5,531,980, a discussion of which is included at the top of page 3 of the current application. From this passage, it can be seen that the system described in Schneider relates to one where air or gas-filled microbubbles "are formed in a suspension of liposomes" (i.e. liquid filled liposomes) and the liposomes apparently stabilise the microbubbles. (See also column 4, lines 18-21, of US 5,643,553). From the aforementioned passages, it will be appreciated by one of ordinary skill in the art that the liposomes of Schneider will inevitably be encapsulated by lipid **bilayers**.

With regard to the targeting of the stabilized microbubbles to particular sites in the body, the Examiner refers to the disclosures on column 9, line 10 onwards. It should be noted in this regard that this passage refers to the binding of monoclonal antibodies to the "phospholipid **bilayers**" (column 9, line 27) and the incorporating of palmitoyl antibodies "**in** phospholipid **bilayers**" (column 9, line 27). These disclosures reinforce the point that the liposomes of Schneider will inevitably be encapsulated by lipid **bilayers**. Furthermore, no specific mention is made in this passage of the use of thiol groups for the binding of the monoclonal antibodies to the surfactant layers. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicants most respectfully submit that Martin (US 5,891,469) does not overcome the deficiencies of the primary references. As can be seen from column 7,

lines 5-13, of the patent, the liposome compositions described in Martin relate only to ones which can form lipid **bilayers**. Thus these vesicles will not possess the advantageous properties of the microbubbles of the invention.

It is respectfully submitted therefore that none of the cited documents, either individually or in combination, would have reasonably suggested to the skilled person the use of a reporter comprising gas-filled microbubbles stabilised by **monolayers** of film-forming surfactant such as that now being claimed. Furthermore, it is particularly asserted that none of the cited documents, either individually or in combination, would have reasonably suggested to the skilled person the use of such reporters having the specific combination of the further features mentioned in the claims. Accordingly, it is most respectfully requested that the prior art rejections be withdrawn.

Applicants wish to note for the record that Unger and Martin were not published as of the filing date of the current invention. It appears to be clear that these references are cited them in an attempt to illustrate the state of the common general knowledge in the art as of 1995-1997.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,
BACON & THOMAS, PLLC

By: Richard E. Fichter
Richard E. Fichter
Registration No. 26,382

625 Slaters Lane, 4th Fl.
Alexandria, Virginia 22314
Phone: (703) 683-0500
Facsimile: (703) 683-1080

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Marked-Up Version Showing Changes Made

IN THE CLAIMS:

Please cancel withdrawn claims 39, 45, 46, 50-62 and 64 without prejudice or disclaimer as directed to a non-elected invention.

Please replace claims 38 and 63 with amended claims 38 and 63.

38(Amended). A targetable diagnostic and/or therapeutically active agent comprising a suspension of a reporter comprising gas-filled microbubbles stabilized by monolayers of film-forming surfactant in an aqueous carrier liquid, and

wherein the gas comprises a halogenated gas or a halogenated [lower] low molecule weight hydrocarbon, and

said film-forming surfactant comprises a phospholipid, and

said agent comprising a lipid attached to a linker portion for covalent coupling to one or more vector molecules, and

where said vector(s) binding to receptors/targets at sites associated with angiogenesis, inflammation, atherosclerotic plaques and/or thrombi,

said linker portion optionally comprising a peptide linker portion.

63(Amended). An agent as claimed in claim 38 comprising a vector which [bindsto] binds to endothelin receptors.